CLINICOPATHOLOGICAL CONFERENCE

Central pontine myelinolysis complicating treatment of multicentric Castleman's disease and Kaposi's sarcoma in a patient with AIDS

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Sex Transm Infect 2003;**79**:179–184

An HIV positive black African woman presented with widespread lymphadenopathy and pancytopenia that had been ascribed to tuberculosis. Lymph node biopsy showed both Kaposi's sarcoma and multicentric Castleman's disease. Despite antiretroviral therapy and chemotherapy the patient deteriorated, developing confusion and dysphasia. A cranial magnetic resonance scan showed central pontine myelinolysis. Despite supportive therapy the patient died.

CASE PRESENTATION
(Dr J Ross)

A 32 years old black African woman from southern sub-Saharan Africa arrived in the United Kingdom in late December 2001. She presented at that time with a 2 week history of intermittent diarrhoea, associated with nausea and intermittent vomiting, anorexia, and weight loss. In August 2001 she had presented in Africa with generalised lymphadenopathy. A presumptive diagnosis of tuberculous lymphadenitis was made; no biopsy was performed to confirm the diagnosis. The patient had been commenced on quadruple antituberculous therapy, with rifampicin, isoniazid, pyrazinamide, and ethambutol. At the same time a diagnosis of HIV infection was made and the patient began dual nucleoside therapy with didanosine and stavudine. On this regimen the patient reported that her HIV viral load was undetectable. Apart from an episode of malaria treated in September 2001 the patient was otherwise well and had no additional past medical history.

On examination, on admission to hospital in December 2001, she was pyrexial (40°C), had generalised lymphadenopathy with firm, non-tender mobile nodes in the axillae, inguinal, and cervical regions. In the abdomen there was 3 cm hepatomegaly and 6 cm splenomegaly.

Initial investigations included urinalysis which revealed proteinuria + but no haematuria. Urea and electrolytes and liver function tests were normal apart from an albumin of 19 (normal = 35–50) g/l and a C reactive protein of 313 (normal = 0–5) IU/l. The haemoglobin was 5.3 (normal = 11.5–16.0) g/dl, the white cell count was 1.6 (normal = 4.0–11.0) $\times 10^9$/l, and a platelet count was 114 (normal = 150–400) $\times 10^9$/l. The blood film showed normochromic red cells, basophilic stippling, occasional spherocytes, and rouleaux formation. A direct Coombs test was positive and a chest radiograph was normal. How do you think she should be further investigated? What would be your initial management?

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Accepted for publication 29 November 2002

DISCUSSANT
(Dr R F Miller)

There are a number of themes here. In summary, this patient arrived in the United Kingdom from sub-Saharan Africa with a recent clinical diagnosis of lymph node tuberculosis and newly diagnosed HIV infection. She seems to be adhering to her medication as judged by the self reported undetectability of the HIV viral load. If she is also taking her antituberculosis drugs then the fact that she has ongoing problems is odd. The fact that she has diarrhoea, anorexia, nausea, and vomiting makes one question if she has been absorbing her medication and if she has in fact been tolerating the treatment.

She is non-specifically unwell and I am struck by the generalised lymphadenopathy and the significant hepatosplenomegaly. I am picking up on some borderline abnormalities already. The albumin is low. The half life of albumin is 28 days, which tells us that something chronic is going on. She is pancytopenic. This is caused by bone marrow infiltration, bone marrow failure, a drug effect, or a combination of the three. The spherocytosis could be hereditary or be due to a dilutional anaemia effect. The basophilic stippling is probably sideroblastic in origin and is likely to be caused by the isoniazid. The positive direct Coombs test could be non- specific and caused by HIV driven polyclonal hypergammaglobulinaemia or a direct effect of the antituberculous treatment. It occurs with streptomycin and isoniazid and uncommonly with rifampicin. Alternatively, the positive Coombs test could be due to a malignancy—for example, a lymphoma. The normal chest radiograph does not exclude active pulmonary tuberculosis in an HIV infected patient.[1]

Could this be HIV associated persistent generalised lymphadenopathy? The good response to the combination antiretroviral therapy makes this unlikely. The lymphadenopathy could also be due to a lymphoma or to a disseminated infection such as tuberculosis, histoplasmosis, leishmaniasis, or human herpes virus type 8 (HHV-8) infection. Given her country of origin histoplasmosis and leishmaniasis are much less likely as they are rarely encountered in this part of the African continent.

It would be important to carry out further investigations in order to rule out active infection. These might include blood cultures for bacteria,

fungi and mycobacteria, microscopy, and culture of stool for bacteria, mycobacteria and protozoa and culture of urine for bacteria and mycobacteria. A lymph node biopsy would provide diagnostic material. An open "surgical" biopsy is preferable to a fine needle aspiration biopsy as it has a higher diagnostic yield.[2] The biopsy specimen should be divided and sent for microbiological culture and also for histology. Other investigations that would have a high diagnostic yield in this situation include a bone marrow aspiration and trephine[3] and a liver biopsy. Percutaneous liver biopsy in HIV infected patients may be associated with an increased morbidity and mortality compared to the general population[4]: if a liver biopsy is necessary in this patient it might be worth considering a transjugular approach, given that she also has pancytopenia. I'd also do a serum cryptococcal latex agglutination (CRAG) test, several thick and thin blood films to rule out malaria and several "hot" stools for ova, cysts, and parasites. There is a need to ascertain her sickle cell status, and a reticulocyte count as well as haptoglobin should be estimated to determine if there is a significant degree of haemolysis occurring. A confirmatory HIV antibody test, a CD4 count, and an HIV viral load are essential.

Management would depend on the results of these investigations but social support should be arranged at this stage.

CASE PRESENTATION
(Dr Ross)

Blood and urine cultures for bacteria, fungi, and mycobacteria were negative. Stool cultures were negative for *Mycobacteria*, *Cryptosporidium* sp, *Microsporidium* sp, and *Clostridium difficile*. Three blood films for malarial parasites were negative. Hepatitis A, B, and C, syphilis, and toxoplasma serology were negative in blood. Past infection with cytomegalovirus was confirmed by detection of cytomegalovirus (CMV) specific IgG antibodies.

Haemoglobin electrophoresis did not reveal any abnormal forms and a glucose-6-phosphate dehydrogenase enzyme assay was normal. The serum CRAG was negative. The CD4 count was 110 cells $\times 10^6$/l, and the HIV RNA viral load was 5000 copies/ml. An abdominal ultrasound confirmed hepatosplenomegaly: no focal lesions were identified either in the liver, the spleen, or elsewhere in the abdomen.

She received 4 units of blood transfusion and was started on nebulised pentamidine for primary prophylaxis of *Pneumocystis jiroveci (*formerly known as *Pneumocystis carinii)* pneumonia.[5] At this stage antiretroviral therapy was modified to stavudine, lamivudine, and efavirenz. A bone marrow aspirate and trephine, a repeat chest radiograph, a computed tomography (CT) scan of the abdomen, and an inguinal lymph node biopsy were performed. After a week in hospital she became apyrexial and the diarrhoea had settled. She was discharged from hospital.

A week later at an outpatient clinic review, she reported a dry cough, anorexia, and malaise. Examination revealed a temperature of 40.4°C, blood pressure = 100/50 mm Hg and the pulse = 135 beats/minute and was regular. The chest was clear and the hepatosplenomegaly was unchanged.

IMAGING
(Dr M J Duddy)

The chest radiograph was normal. The abdominal computed tomograph (CT) scan was performed with oral contrast. It shows an enlarged liver and spleen (fig 1A). There are also enlarged lymph nodes around the hilum of the spleen and shotty para-aortic lymph nodes (fig 1B).

DISCUSSANT
(Dr Miller)

I agree there is gross hepatosplenomegaly with enlarged lymph nodes and I wonder if there are peritoneal deposits visible on the CT scan? This would make one wonder about mycobacterial infection, a lymphoma, a non-malignant lymphoproliferative process, an ovarian tumour, or even Kaposi's sarcoma.

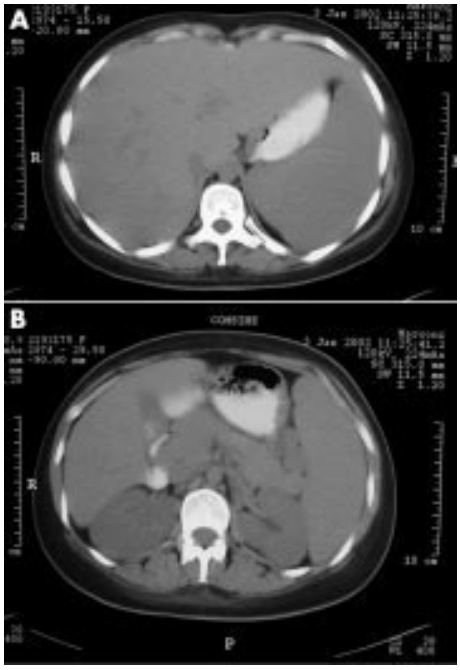

Figure 1 (A) CT of the abdomen 3 January 2002 showing hepatosplenomegaly. (B) CT of the abdomen showing abdominal lymphadenopathy.

CASE PRESENTATION
(Dr Ross)

The bone marrow biopsy showed hyperplastic erythropoiesis with no evidence of lymphoma or mycobacterial infection. The inguinal lymph node biopsy was suggestive, but not diagnostic, of nodal Kaposi's sarcoma and so a cervical lymph node biopsy was arranged in order to make a definitive diagnosis.

The patient was unwell at this stage and had to be re-admitted to hospital where her diarrhoea persisted. The haemoglobin had fallen to 5.1 g/dl, the platelet count = 54×10^9/l, and the white cell count = 1.8×10^9/l. Urea and electrolytes were normal except for a low sodium of 125 (normal =135–145) mmol/l and liver function tests showed aspartate transaminase = 61 (normal= 5–35) IU/l, alkaline phosphatase = 351 (normal = 30–300) IU/l, and the serum albumin = 19 (34–51) g/l. The plasma osmolality was 275 mOsmol/l and urine osmolality was 375 mOsmol/l.

DISCUSSANT
(Dr Miller)

There is something odd here. A hyperplastic marrow with pancytopenia which is getting worse and low plasma sodium. Could this be due to Addison's disease? Are the adrenals so small as not to be seen on a CT scan? Could they be infected by HIV, CMV, or *Histoplasma capsulatum*—or is this just a syndrome of inappropriate antidiuretic hormone secretion which would fit with the low plasma sodium and plasma osmolality. It could also be panhypopituitarism with secondary hypothyroidism. I would like to check her urinary sodium excretion. I would also like to check her thyroid function, and luteinising hormone and follicle stimulating hormone levels in order to assess the hypothalamic-pituitary axis. I would like to know more about the histology of the bone marrow biopsy. Was there an excess of any particular cell line—for example,

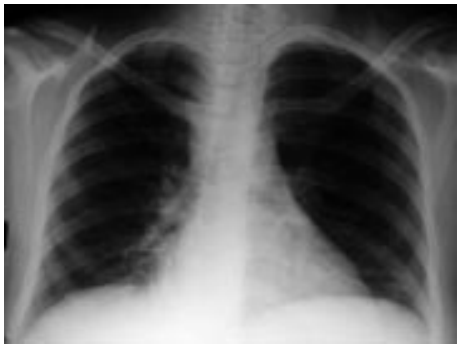

Figure 2 PA chest radiograph (rotated) 16 February 2002 showing right middle lobe atelectasis and right paratracheal widening.

plasma cells? Was the marrow infiltrated elsewhere by malignancy that was not picked up on this sample? I wonder if the lymph nodes are co-involved with another malignant or infective process?

She has probable Kaposi's sarcoma so she is infected with HHV-8. Could she have an HHV-8 associated body cavity lymphoma? Could she have multicentric Castleman's disease, which is associated with HHV-8 and can co-exist with Kaposi's sarcoma or a lymphoma?[6]

CASE PRESENTATION
(Dr Ross)

With rehydration the plasma sodium improved. The infection screen was repeated and a cervical lymph node biopsy was carried out. The patient's condition did not improve, the diarrhoea persisted, she became more confused and the clotting screen became abnormal, with an increased activated partial thromboplastin time (APTT) ratio of 1.7, international normalised ratio (INR) of 1.4, and *d*-dimers > 250 IU.

Blood cultures grew *Salmonella enteritidis,* which was treated with intravenous cefotaxime and gentamicin, followed by oral ciprofloxacin. She also received a further 4 units of blood transfusion. The patient's clinical condition improved: her temperature settled to between 37°C and 38°C, but her appetite remained poor and she continued to lose weight. The dry cough persisted.

IMAGING
(Dr Duddy)

The chest radiograph was abnormal (fig 2). The film is rotated; however, the right heart border is effaced and there is patchy atelectasis in the right lower zone, presumably in the middle lobe. There is right paratracheal widening with loss of the right para-tracheal stripe.

CASE PRESENTATION
(Dr Ross)

A bronchoscopy was performed in order to further investigate the radiographic abnormalities. The airways appeared normal and microscopy and culture of lavage fluid were negative for bacteria, mycobacteria, and fungi, including *P jiroveci*. No CMV DNA was detected in serum using a quantitative polymerase chain reaction (PCR) assay.

PATHOLOGY
(Dr V Mudaliar and Professor E L Jones)

The inguinal lymph node shows capsular fibrosis, reactive follicular hyperplasia, and neovascularisation. Some lymphoid follicles are small with "naked" germinal centres consisting of follicular dendritic cells associated with hyalinised vessels within the centres (Fig 3A). These germinal centres are surrounded by a dense mantle of small lymphocytes with

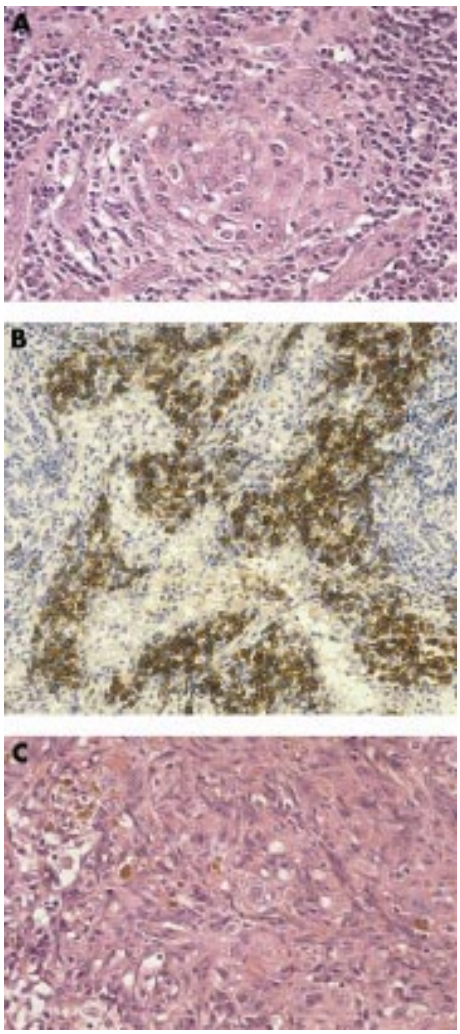

Figure 3 (A) Inguinal lymph node showing vascularised hypocellular germinal centre. Haematoxylin and eosin. Magnification ×100. (B) Inguinal lymph node showing interfollicular zone plasma cells. Strept ABC immunostained for CD138. Magnification ×100. (C) Inguinal lymph node showing proliferating spindle cells, around slit-like vascular channels representing Kaposi's sarcoma. Haematoxylin and eosin. Magnification ×100.

scattered plasma cells and "plasmablasts" within the mantle. In the interfollicular zones there is a dense population of plasma cells associated with high endothelium venular proliferation. The features are those of the plasma cell variant of Castleman's disease.

On immunohistological staining the plasma cells in the interfollicular zones (fig 3B) show polytypic expression of immunoglobulin light chains with roughly equal numbers of kappa and lambda positive cells. These plasma cells also show nuclear positivity for HHV-8. Within the hypocellular germinal centres and mantles the scattered plasma cells show monotypic expression of lambda light chain only. These scattered mantle cell plasma cells also show nuclear HHV-8 staining.

Elsewhere in the node the sinuses are disrupted by proliferating spindle cells forming slit-like vascular spaces (fig 3C) with extravasion of red blood cells and scattered haemosiderin pigment deposition. The spindle cells express the vascular marker CD34 and occasional nuclei focally express HHV-8. These features are in keeping with nodal Kaposi's sarcoma. Similar appearances can be seen in a reactive condition known as vascular transformation of lymphatic sinuses, which usually occurs in inguinal lymph nodes and the other changes

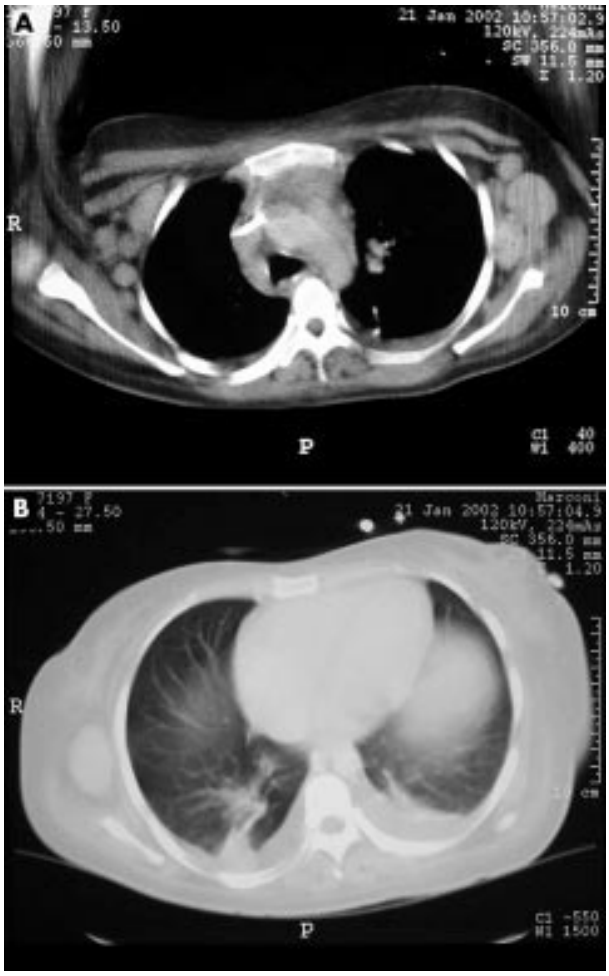

Figure 4 (A) and (B) CT of the chest 21 February 2002 shadowing gross axillary lymphadenopathy, bilateral pleural effusions, and basal passive atelectasis.

of VTLS including sclerosis and ossification may make differentiation from Kaposi's sarcoma difficult. A further lymph node biopsy from another site was recommended. A cervical lymph node showed more extensive changes of Kaposi's sarcoma.

The inguinal node also shows HIV related changes with follicululolysis and an immunostain for the HIV p24 antigen showed positivity on the follicular dendritic cells.

In summary, the features are those of HHV8- associated plasma cell variant of Castleman's disease, nodal Kaposi's sarcoma, and HIV.

IMAGING
(Dr Duddy)
A CT scan of the thorax and abdomen was carried out without intravenous contrast. This showed striking axillary lymphadenopathy and also some para-tracheal lymphadenopathy. In addition there were small bilateral pleural effusions with underlying passive atelectasis (figs 4A and B). There was also marked hepatosplenomegaly.

DISCUSSANT
(Dr Miller)
What strikes me is the absence of features consistent with what we know about this woman so far. Kaposi's sarcoma in the lungs gives rise to interstitial changes and the hallmark of this is fissural and parenchymal nodularity,[7] which is absent here. I am intrigued by the wedge-shaped area at the right lung base which could be due to a pulmonary infarct or atelectasis.

So far we have got lymphadenopathy, atelectasis, pleural effusions, and not much else going on in the lungs. It would be important to perform a pleural aspiration and biopsy, perhaps under ultrasound guidance in order to exclude co-pathology such as lymphoma or tuberculosis.

If we can rule out co-pathology then she needs treatment for a disseminated HHV-8 driven disease, which here is the Kaposi's sarcoma and the Castleman's disease, in addition to treatment of her HIV disease.

CASE PRESENTATION
(Dr Ross)
Things got difficult at this point as the patient declined further interventions and expressed a wish to return to Africa. After a few days she agreed to the insertion of a Hickman line. Her symptoms of intermittent vomiting, fever, and diarrhoea persisted and she developed pitting ankle oedema.

It was planned to give her vincristine and bleomycin as treatment of both the Kaposi's sarcoma and the Castleman's disease. Before this could be commenced she developed septicaemia secondary to the Hickman line; this was treated with intravenous vancomycin. She later developed methicillin resistant *Staphylococcus aureus* (MRSA) septicaemia, which was treated with oral rifampicin and intravenous vancomycin.

Soon after the first cycle of chemotherapy, she developed painful feet and lower legs. Nerve conduction studies demonstrated a mixed motor and sensory neuropathy.

At this stage the CD4 count = 140×10^6/l and the HIV viral load was >75 000 copies/ml. An HIV genotypic resistance test was performed. This showed that the L74L/V, K101E/K, K103N, V106M, and G190mix reverse transcriptase mutations were present. In addition the L63T, A71T, V77I, and I93L protease gene mutations were identified. This was interpreted as showing susceptibility to zidovudine, stavudine, lamivudine, tenofovir, and all protease inhibitor drugs. The virus was resistant to non-nucleoside reverse transcriptase inhibitors as the K103 mutation was present.

DISCUSSANT
(Dr Miller)
I would actually stop the antiretroviral drugs at this stage. I do not think it will be feasible to treat her with chemotherapy for the Kaposi's sarcoma and Castleman's disease and at the same time give her antiretrovirals.

CASE PRESENTATION
(Dr Ross)
We decided to change her antiretroviral regimen to tenofovir, lamivudine, and ritonovir/lopinavir, in the light of the findings of the genotypic resistance assay. Following the chemotherapy she improved clinically, her lymphadenopathy reduced, she became apyrexial and her anorexia and appetite improved.

The peripheral neuropathy progressed and involved her hands as well as her feet. Over the next week or so she became more confused and developed slurred speech. A careful neurological examination revealed no focal signs. A cranial CT scan was performed.

IMAGING
(Dr Duddy)
An unenhanced cranial CT scan shows a well defined rounded area of reduced attenuation in the centre of the pons. The fourth ventricle and the pentagonal cistern are unaffected by this lesion (fig 5).

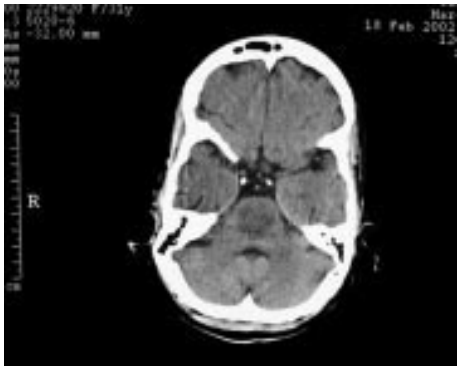

Figure 5 CT of the head (unenhanced) showing central pontine low attenuation lesion.

CASE PRESENTATION
(Dr Ross)

A cranial magnetic resonance image (MRI) was performed, in order to try and identify the cause of the CT abnormality. Following a second course of chemotherapy with vincristine and bleomycin a pancytopenia developed which required support with granulocyte colony stimulating factor, immunoglobulin, and transfusion of platelets and blood.

IMAGING
(Dr Duddy)

This T1 weighted axial MR image at the same level in the brain shows a rounded area of low signal intensity in the pons (fig 6A). This lesion is of high signal intensity on the T2 weighted image and the proton density image shows a midline symmetrical lesion (fig 6B). A mid sagittal image shows the lesion to be confined to the pons (fig 6C). There were no lesions elsewhere in the brain. The pre-pontine cistern is unperturbed and the fourth ventricle unaffected by this lesion. The T1 weighted gadolinium enhanced images do not show any significant contrast enhancement.

DISCUSSANT
(Dr Miller)

I think that that the cranial MRI scan shows the "bat's wing" or "trident" sign.[8] The lesion in the pons appears well demarcated and the irregular lower edge is because the VIth cranial nerve nuclei (which are white matter) are not involved by this process. What we need to do now is to construct a differential diagnosis. Clinically here is someone who has been unwell for some time, with a poor food intake, who has a low sodium, a low albumin, and who has been receiving chemotherapy. The cranial MRI shows no meningeal or dural reaction, which goes against a diagnosis of tuberculosis or sarcoid granuloma in the pons. There is no other abnormality elsewhere in the hemispheres, just a single lesion in the pons, which does not expand the pons, extend out of it, or enhance with contrast.

What could it be? She is not that unwell to have a brainstem infarct and she does not have cranial nerve lesions. Could this be brainstem encephalitis, which could be due to herpes zoster or cytomegalovirus? Yes, but they would also affect adjacent cranial nerves, which is not happening here. Could this be a pontine glioma? This occurs most frequently in younger people, particularly boys, but it also tends to affect the VIth cranial nerve. It could also be an astrocytoma or a secondary cancer. However, there is no evidence of a primary lesion on clinical examination and on imaging. Radiotherapy may give rise to this sort of lesion but the patient has not been treated with radiotherapy. Chemotherapy may also produce this kind of lesion; cyclophosphamide in particular has been implicated in this context. Could these appearances be due to multiple sclerosis? This is unlikely to present with a single lesion. This could also be progressive multifocal leucoencephalopathy (PML), which can occur at a variety of CD4 counts and may present with a single lesion if it involves an important part of the brain.

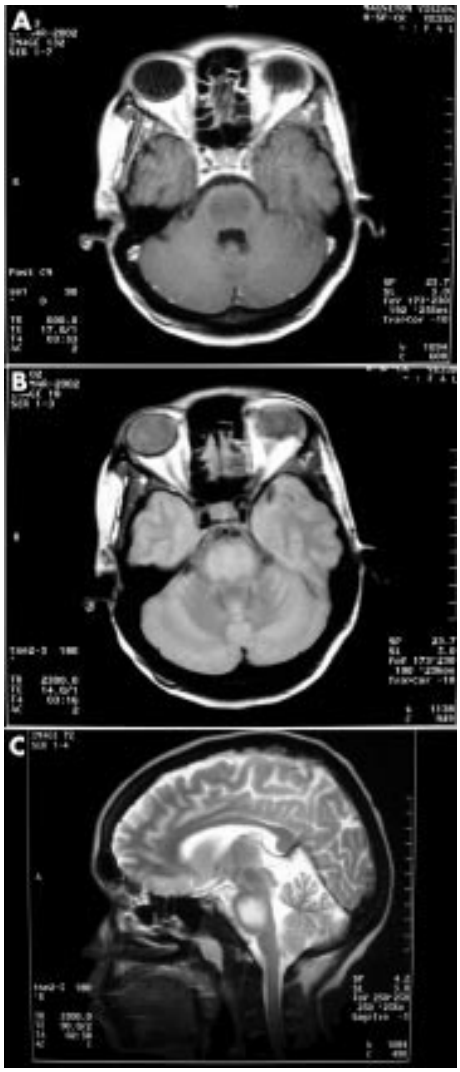

Figure 6 (A) MRI showing pontine lesion of low signal intensity on axial T1 weighted imaging. (B) MRI proton density image showing the central symmetrical "bat's wing" nature of the pontine lesion. (C) Sagittal MRI scan showing pontine lesion of high signal intensity on T2 weighted imaging.

Could this be focal pontine leucoencephalopathy, which is an HIV related condition producing vacuolation in the pons and mimicking changes seen in both HIV associated vacuolar myelopathy and subacute combined degeneration of the cord?[9] Could this be due to acute demyelinating encephalomyelitis? This is unlikely as there is no antecedent history, apart from sepsis.

I think that this is central pontine myelinolysis producing this symmetric demyelination of the pons. Further investigations are needed to rule out alternative causes of focal demyelination. This would include looking for herpesvirus and JC virus DNA, by means of PCR, in cerebrospinal fluid obtained at lumbar puncture.

My differential diagnosis is central pontine myelinolysis secondary to her chronic illness, or possibly a focus of PML.

IMAGING
(Dr Duddy)

In an HIV patient with a brain lesion the diagnosis will be primary lymphoma, toxoplasmosis, or PML in more than 90% of

cases. However, these are effectively excluded in this case by the unifocal nature of the lesion, the lack of mass effect, and the lack of significant contrast enhancement.

Given the clinical features and the typical MRI appearances, the most likely diagnosis is central pontine myelinolysis.

CASE PRESENTATION

(Dr Ross)

The patient was given systemic corticosteroids and further chemotherapy was planned. Venous access and recurrent septicaemia remained problematic. The neuropathy worsened, as did the pancytopenia. A third cycle of chemotherapy, with vincristine and bleomycin was given; subsequently there was marked clinical deterioration. The patient became increasingly confused, developed steroid induced diabetes requiring an insulin infusion, and developed an MRSA septicaemia, which was treated with intravenous vancomycin and oral rifampicin. She had several epistaxes due to the thrombocytopenia, diarrhoea due to *Clostridium difficile* infection, and herpetic genital ulceration. A subcutaneous diamorphine infusion was commenced in order to palliate her symptoms and she died shortly thereafter. A request for a necropsy examination was refused by the patient's relatives.

DISCUSSANT

(Dr Miller)

Central pontine myelinolysis was first identified as an entity in 1949. Adams and Victor, two neurologists at Boston City Hospital, cared for a 38 year old chronic alcoholic man who was admitted to hospital with a lobar pneumonia and delirium tremens. After an initial clinical recovery, on day 9 the patient deteriorated steadily over 48 hours—with the development of a flaccid quadriplegia, facial weakness, and an inability to speak or swallow. Necropsy revealed a sharply demarcated symmetrical focus of demyelination in the centre of the pons. This involved all fibre tracts, but spared nerve cells and axis cylinders. Three further cases were identified by these neurologists over the next few years, two with chronic alcoholism and one with chronic malnutrition. All had similar neurological features and necropsy findings.[10]

Subsequently there have been many reports of central pontine myelinolysis. Every case described has been associated with a severe underlying disorder, such as chronic alcoholism, chronic renal failure and dialysis, hepatic failure, disseminated malignancy, severe sepsis, malnutrition/cachexia from a variety of causes, burns and hyponatraemia from any cause—particularly when the hyponatraemia is corrected rapidly. It has been suggested that in most cases central pontine myelinolysis arises because of osmotic demyelination and this is likely to occur when there is rapid (>12 mmol/l/24 hours) correction of hyponatraemia.[11] In burns patients who develop central pontine myelinolysis, it is the intercurrent hyperosmolar state that is thought to be the cause.

Central pontine myelinolysis has been described in patients with HIV infection; it is frequently not recognised in life.[12–15] In addition to their HIV infection, all patients also had other severe chronic illnesses, including malignancy (Kaposi's sarcoma or lymphoma), chronic alcoholism, or infection. The clinical presentation of central pontine myelinolysis is similar in those who have underlying HIV infection and in those who do not. Features range from a rapidly evolving flaccid paraparesis with a pseudobulbar palsy, to changes in mental state or personality, with or without associated confusion, and coma.[10–15] Some cases are clinically silent and are only diagnosed at necropsy.[14 15]

Key points

(1) Multicentric Castleman's disease should be included in the differential diagnosis in HIV infected patients presenting with generalised lymphadenopathy, hepatosplenomegaly, and pancytopenia.
(2) More than one pathological process may co-exist in a biopsy specimen—in this case HIV infection, Kaposi's sarcoma, and plasma cell variant Castleman's disease.
(3) Central pontine myelinolysis may occur in association with a variety of chronic debilitating illnesses—in this case Castleman's disease, the treatment thereof, and recurrent sepsis.

FINAL DIAGNOSES

(1) Plasma cell variant multicentric Castleman's disease

(2) Kaposi's sarcoma

(3) Central pontine myelinolysis.

A Apoola and M Huengsberg contributed significantly to the management of the patient, preparing the CPC, and writing up the paper.

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